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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,688	01/07/2002	Yong Hua Zhu	LOMAU.143A	5449

20995 7590 03/23/2004

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EXAMINER

GHALI, ISIS A D

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 03/23/2004

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/041,688

Applicant(s)

ZHU ET AL.

Examiner

Isis Ghali

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8-18 and 20-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-18, 20-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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DETAILED ACTION

The receipt is acknowledged of applicants' amendment C and formal drawings, both filed 01/20/2004.

Claims 7 and 19 have been canceled, and claims 25-34 have been added per applicant's amendment B.

Claims 1-6, 8-18, 20-34 are included in the prosecution.

The following new ground of rejections are necessitated by applicant's amendment:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 25-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites the limitation "substance" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

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Claim 30 recites the limitation "substance" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Regarding claims 27-29, and 31-34, the claims are vague as they recite: "microencapsulated antibiotics comprises gelatin microcapsules", and this reads as the microcapsules comprises gelatin microcapsules included inside microcapsules. Recourse to the specification showed that the microcapsules that encapsulate the antibiotics are made of gelatin, page 11 and 30 of the present specification. Clarification is requested.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 4, 5, 8, 9, 12, 13, 16, 17, 20, 21, 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/10374 ('374) in view of US 4,919,939 ('939).

WO '374 discloses *in situ* polymerizing (*in situ* curing) biomedical implant material and a method for repair of mammalian tissue using the same biomedical material (abstract; page 8, line 35; page 9, line 1). The material comprises cyanoacrylate adhesive, hydrophilic porosifying agent and antibiotic (page 6, lines 9, 16-17; page 7, line 1; page 8, line 23 till page 9, line 2). The hydrophilic porosifying agent includes polyethylene glycol that dissolve *in situ* as a result of exposure to an aqueous environment, e.g. body fluids are aqueous (page 4, lines 20-23). The *in situ* polymerizing implant material is introduced into the repair site (reads on wound) by variety of means and is used as a sealant in anatomic regions where it would be difficult to use a pre-cast dressing (page 12, lines 12-19). Introducing the *in situ* polymerizing implant material into the repair site reads on the step of "approximating the wound" in claim 12. Polymerization *in situ* reads on the step of curing the adhesive in claim 12.

The reference teaches encapsulating the active substance or the material of the capsule. The reference does not teach that the porosifying agent dissolves in the aqueous environment, i.e. the body fluid, but the reference does not teach the delivery of the substance to the tissue.

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It is implied in the teaching of the reference in the teaching of the pre-cast system in the form of occlusive dressing or burn dressing that they deliver active agents such as anti-microbials (page 12, lines 22-30). It is expected from the implanted composition that polymerize *in situ* and comprises hydrophilic pore forming agent and substance to deliver the substance through the pores after the pore-forming agent dissolves.

US '939 teaches a controlled release and self retaining drug delivery device that incorporate drug-containing microcapsules in fluid carrier medium and is effective in the environment of use up to 30 days (abstract; col.1, lines 16-18; col.4, lines 1-3). The microcapsules contain antibiotics such as penicillin and amoxicillin (col.5, lines 44, 52-56). The microcapsules comprise gelatin (col.7, line 7). The microcapsules are incorporated in a matrix of cyanoacrylate (col.11, line 15).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a composition and a method for sealing wound comprising approaching the wound and applying composition comprising cyanoacrylate, pore forming agent and encapsulated active substance where the substance is delivered via the pores formed by removal of the pore forming agent, because WO '374 teaches that the substance to be delivered can be antibiotics that control sepsis of the wound, as desired by applicants, and further provide the active substances encapsulated in gelatin as disclosed by US '939, motivated by the teaching of US '939 that encapsulated active agent provide controlled release of the active agent, with reasonable expectation of the delivered wound sealing composition and method not

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only to seal the wound, but also deliver antibiotic to prevent its sepsis with the subsequent drawbacks.

6. Claims 2, 3, 14, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view of US '939 and further in view of US 5,811,091 ('091).

The teachings of WO '374 in view of US '939 are discussed above.

WO '374 in combination with US '939 do not teach the cyanoacrylate as butyl or octyl cyanoacrylate as in claims 2, 3, 14, and 15.

US '091 teaches a composition comprising cyanoacrylates with the most preferred compounds include butyl and octyl cyanoacrylate because they bond the human skin tissue without causing histotoxicity or cytotoxicity (col.5, lines 26-49). The composition is useful for topically covering non-suturable wounds (col.8, line 4).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to deliver the composition for wound sealing comprising cyanoacrylate, pore forming agent and encapsulated active substance as disclosed by WO '374 in view of US '939, and select butyl and octyl cyanoacrylate as taught by US '091, motivated by the teaching of US '091 that the butyl and octyl cyanoacrylate bond the human skin tissue without causing histotoxicity or cytotoxicity, with reasonable expectation of having a safe compatible wound sealing composition that successfully seals non-suturable wounds.

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7. Claims 2, 3, 10, 11, 14, 15, and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view of US '939 and further in view of WO 96/00760 ('760).

The teachings of WO '374 in view of US '939 are discussed above.

WO '374 in view of US '939 do not teach the cyanoacrylate as butyl or octyl cyanoacrylate as in claims 2, 3, 14, and 15; the anti-degradation agents claimed in claims 10, 11, 23 and 24; or the wound as a lacerated wound as in claim 22.

WO '760 teaches a biocompatible composition comprising pH modifier and cyanoacrylate monomer useful as biomedical and surgical adhesive and sealant (abstract; page 5, line 17). The advantageous monomers of the composition are butyl and octyl cyanoacrylate, as claimed in claims 2, 3, 14, 15, as they form a composition of adequate flexibility and strength to withstand normal movement of the tissue and a bond strength that is maintained as natural tissue healing proceeds (page 6, lines 15-19; page 18, lines 23-32). The pH modifier regulates the polymer biodegradation by regulating the pH of the in vivo environment of the biocompatible composition and makes it proceeds more slowly than it does at a physiological pH, this reads on anti-degradation agents claimed in claims 10 and 23, resulting in retarding the rate of release of the degradation products, thereby reducing their toxic effects (page 3, lines 27-29; page 9, lines 28-35). PH modifiers include ascorbic aid (vitamin C), claimed in claims 11 and 24 (page 10, line 26). The compositions of the reference find uses in traumatically lacerated tissues, claim 22 (page 4, lines 6-12).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound using composition comprising cyanoacrylate, pore forming agent and encapsulated active substance as disclosed by WO '374 in view of US '939 and select the octyl and butyl cyanoacrylate monomers as they are preferred by WO '760 because the compositions comprising them are useful as tissue adhesive or sealants that find uses in traumatically lacerated tissues, a function desired by applicants, and they form a composition of adequate flexibility and strength that is maintained as natural tissue healing proceeds, and also one having ordinary skill in the art would have been motivated to add anti-degradation agents such as vitamin C disclosed by WO '760 to the sealing composition of WO '374 in combination with US '939 motivated by the teaching of WO '760 that these compounds regulate the polymer biodegradation and make it proceeds more slowly than it does at a physiological pH resulting in retarding the rate of release of the degradation products, thereby reducing their toxic effects with reasonable expectation of having safe non toxic wound sealant with sustained sealing effect.

8. Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view US '939 and further in view of WO 99/20685 ('685).

The teachings of WO '374 in view of US '939 are discussed above.

WO '374 in view of US '939 do not teach the molecular weight of the polyethylene glycol as claimed in claims 6 and 18.

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WO '685 teaches a formulation that forms a film comprising water soluble pore forming agent such as polyethylene glycol that leaches out through the film in situ and creates a perforations that regulate the release rate of active agents (page 7, lines 10-16). The preferable molecular weight of the polyethylene glycol that is able to create adequate pore size for controlling the release of the active agents is from 540 to 8000, i.e. encompasses the molecular weight claimed by applicants in claims 6 and 18 (page 9, lines 23-28; page 10; lines 1-2).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound using composition comprising cyanoacrylate, polyethylene glycol as pore forming agent and encapsulated active substance as disclosed by WO '374 in view of US '939 and select the molecular weight of the polyethylene glycol between 540 and 8000 as taught by WO '685 because this range of molecular weight is preferred by the WO '685 because of the ability of polyethylene glycol having such molecular weight to create adequate pore size for controlling the release of the active agents, with reasonable expectation of success of the delivered wound sealing composition to deliver active agents at a controlled rate to the wound site with success.

Response to Arguments

9. Applicant's arguments with respect to claim 1-6, 8-18, 20-24 have been considered but are moot in view of the new ground(s) of rejection. The main gist of

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applicant rejection was the cited prior art do not teach the encapsulated active agent.

The new grounds of rejections render the claims obvious.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis Ghali
Examiner
Art Unit 1615

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